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Schistocytosis and a Thrombotic Microangiopathy-Like Syndrome in Hospitalized HIV-Infected Patients

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Approximately 150 human immunodeficiency virus (HIV)-infected patients with a thrombotic microangiopathy (TMA)-like syndrome have been reported in the literature since the early 1980s. The prevalence of a TMA-like syndrome in our hospitalized patients was determined to discern whether it is a more common occurrence than previously recognized and, if possible, to delineate risk factors for its occurrence. A total of 350 patients admitted consecutively to the Johns Hopkins Hospital HIV inpatient service were assessed from May 1, 1996 through February 1, 1997. These patients were evaluated for the presence of anemia, thrombocytopenia, fragmented erythrocytes on peripheral blood smear (schistocytosis), renal dysfunction, neurologic dysfunction, and fever. The association of a TMA-like syndrome with demographic and clinical factors was analyzed. Schistocytosis was present in 24% of the patients and a TMA-like syndrome (anemia, thrombocytopenia, schistocytosis + renal dysfunction or neurologic dysfunction, and fever) was present in 7% of the patients. The patients who had a TMA-like syndrome were more likely to have a low CD4 lymphocyte count or CD4 percentage, Centers for Disease Control and Prevention stage C disease, and have bacterial sepsis. Age, race, HIV risk group, other diagnoses, and prescribed drugs were not associated. Patients were more likely to die if they had a TMA-like syndrome, independently of level of immunosuppression. Schistocytosis and a TMA-like syndrome are relatively common in hospitalized HIV-infected patients. This syndrome may contribute to mortality and morbidity, particularly in patients with more advanced disease. Am. J. Hematol. 60:116–120, 1999.

Key words: schistocytosis; thrombotic microangiopathy; HIV; AIDS

INTRODUCTION

Thrombotic thrombocytopenia purpura (TTP) and hemolytic uremia syndrome (HUS) are considered to be part of a spectrum of diseases collectively known as thrombotic microangiopathy (TMA) [1,2]. An association between TTP and human immunodeficiency virus (HIV) was first recognized as early as 1984 [3], with the first definitive report of this association in 1988 [4]. TMA or a TMA-like syndrome has now been reported in about 150 patients [5]. However, TMA may be difficult to diagnose in HIV-infected patients due to the high probability of pre-existing conditions that can mimic many of the clinical features of TMA. These clinical features include thrombocytopenia, anemia, fever, neurologic and renal abnormalities, and erythrocytic fragmentation. A recent series described a 14% prevalence of HIV infection in patients diagnosed with TTP or HUS [6]. Unfortunately, there are very little natural history data available regarding the prevalence of TMA in patients with HIV infection. In particular, the frequency of erythrocytic fragmentalization, an important feature of TMA among HIV patients, is unknown because examination of the peripheral red blood cell smear is not commonly a part of the routine clinical evaluation. A prospective study to better quantitate the prevalence of

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erythrocytic fragmentation, and the frequency of associated signs and symptoms characteristic of TMA or a TMA-like syndrome was conducted.

METHODS

Data Collection

From May 1, 1996 through February 1, 1997, consecutive patients admitted to the Johns Hopkins Hospital HIV/AIDS inpatient unit were asked to participate in a study of the frequency of schistocytosis (fragmented erythrocytes) in HIV-infected patients. All HIV-infected patients admitted to this service were eligible to participate with no exclusions. If a patient was cognitively impaired, consent was obtained from a family member or significant other. Fewer than 2% of the patients (or surrogate) refused consent.

After written informed consent was obtained, a peripheral blood smear was obtained on the patient. This sample was obtained within 24 hr of the time that informed consent was given and within 72 hr of admission to the hospital (median time = 24 hr). The blood smear was examined microscopically in the Johns Hopkins Hospital Hematology Laboratory and a qualitative assessment was made of the presence of fragmented erythrocytes. According to laboratory criteria, these were graded as follows: 0 = absent; 1 = occasional fragmented cell seen (less than one per high-powered field); or 2 = one or more fragmented cells seen in most high-powered fields. The hematology laboratory technologists who evaluated these blood smears were not aware that these patients were HIV seropositive.

Demographic, clinical, and other laboratory information was abstracted from the patient's hospital records. Diagnoses were those determined clinically by the provider of care. Pharmaceuticals were recorded as being used if the patient was actively using the drug on admission. The patient was followed until the end of hospitalization to determine length of stay and vital status at discharge.

Definitions

Fever was defined as a body temperature $\geqslant$37.5°C. Renal dysfunction was defined as a serum creatinine >1.4 mg/dl, or proteinuria defined as 1+ or greater protein on urine dipstick, or hematuria was as 1+ or greater hemoglobin on urine dipstick. Neurologic dysfunction was defined as a motor deficit (defined as weakness (<5 on a 5-point scale) in one or more muscle groups on physical exam), sensory deficient (defined as diminished pain, light touch, or vibration), cognitive deficit (defined as any level of decreased sensorium on the Glasgow Coma Scale), focal or generalized seizure or a headache. Anemia was defined as a hemoglobin level <12 gm/dl in men or <11 gm/dl for women. Thrombocytopenia was defined as a platelet count <150,000/mm^3. Schistocytosis was defined as grade 2 fragmented erythrocytes. A TMA-like syndrome was defined as having anemia, thrombocytopenia, schistocytosis, and either renal dysfunction or neurologic dysfunction and fever. These criteria were based on the work of Bell et al. [5].

TABLE I. Characteristics of Enrolled Patients*

Age (years)	39 (20–68)[a]
Sex	
Male	242 (69%)[b]
Female	108 (31%)
Race	
White	54 (15%)
African American	286 (82%)
Other	10 (3%)
HIV risk[c]	
IDU	206 (59%)
Homosexual	81 (23%)
Heterosexual	132 (38%)
Other	22 (6%)
CDC stage	
A	8 (2%)
B	90 (26%)
C	252 (72%)
CD4 count (cells/mm^3)	36 (0–1141)
HIV-1 RNA (copies/ml)	94,000 (undetectable—>1 million)
Length of stay (days)	5 (3–51)
Creatinine (mg/dl)	0.9 (0.4–17.4)
Hemoglobin (g/dl)	
Male	11.0 (5.2–15.2)
Female	10.3 (4.1–17.9)
Platelet count (/mm^3)	206,000 (6,000–673,000)
White blood count (cells/mm^3)	4,750 (500–29,200)

*IDU, injecting drug use; HIV, human immunodeficiency virus; CDC, Centers for Disease Control and Prevention.
[a]Median (range).
[b]Number (percentage).
[c]Overlap between IDU and sexual, therefore does not add to 100%.

Analysis

Descriptive analysis was done of the characteristics of all the patients enrolled. Demographic, clinical, therapeutic, and laboratory information was compared between those who had a TMA-like syndrome and those who did not, using appropriate statistical tests. This included the chi-square for proportions and the Student's *t*-test for continuous variables. Multivariate analysis was done using backward stepwise logistic regression. All analyses were done using SAS software (SAS, Inc., Cary, NC).

RESULTS

A total of 350 patients were enrolled in this study. The demographic and clinical characteristics of the patient sample are shown in Table I. Grade 2 schistocytosis was found in 84 patients (24%). The remaining 266 patients had absent or only rare (grade 0/1) fragmented erythrocytes. We first examined the association between grade 2 schistocytosis and the occurrence of other possible manifestations of TTP (Table II). Associated characteristics

TABLE II. Features of TTP in Patients With and Without Schistocytosis*

TTP features in patients	Schistocytosis: Yes (n = 84)	Schistocytosis: No (n = 266)	*P* value
Neurologic			
Motor deficit	26 (31%)	60 (23%)	.13
Sensory deficit	24 (29%)	62 (23%)	.34
Cognitive deficit	19 (23%)	34 (13%)	.03
Seizure	5 (6%)	12 (5%)	.60
Headache	21 (25%)	78 (29%)	.43
Fever (⩾37.5°C)	44 (52%)	159 (60%)	.23
Proteinuria (⩾1 + protein)	40 (65%)	118 (56%)	.40
Hematuria (⩾1 + hemoglobin)	36 (58%)	113 (54%)	.31
Creatinine >1.4 mg/dl	28 (33%)	64 (24%)	.09
Any renal disease	63 (75%)	175 (66%)	.12
Thrombocytopenia (<150,000/mm^3)	29 (35%)	74 (28%)	.24
Anemia (<11 g/dl women; <12 g/dl men)	66 (79%)	155 (58%)	.001
Anemia + thrombocytopenia (group 1)	27 (32%)	49 (18%)	.008
Group 1 + renal disease	22 (26%)	32 (12%)	.002
Group 1 + neurologic + fever	8 (10%)	19 (7%)	.48
LDH (units/ml)[a]	398 ± 268 (n = 16)	352 ± 199 (n = 44)	.47
Reticulocytes(%)[a]	1.2 ± .9 (n = 10)	1.2 ± .9 (n = 31)	.99

*TTP, thrombotic thrombocytopenia purpura; LDH, lactate dehydrogenase.
[a]Not available on most patients.

were a cognitive neurologic deficit and anemia. The features that define a TMA-like syndrome are shown in Table III. A total of 25 patients (7%) fulfilled the criteria for a TMA-like syndrome. The associations of the various patient characteristics and TMA-like syndrome are shown in Table IV. The associations between the drug received and the diagnosis made and a TMA-like syndrome are shown in Table V. Only bacterial sepsis was associated with a TMA-like syndrome. Of note, no patient was diagnosed with disseminated intravascular coagulation (DIC), and no patient had metastatic malignant disease. Associated factors included Centers for Disease Control and Prevention (CDC) stage C HIV disease, a low absolute CD4 count or CD4 percentage, and a diagnosis of bacterial sepsis. Patients with a TMA-like syndrome were more likely to die within 30 days.

Multivariate analysis showed that low absolute CD4 count and bacterial sepsis were independently associated with a TMA-like syndrome ($P < .01$ for each). Adjusting for these two variables, no other demographic or clinical variable including diagnosis or specific drug was associated with a TMA-like syndrome. A second multivariate analysis showed that having a TMA-like syndrome was associated independently with death (relative odds = 4.46; 95% CI: 1.54, 12.46; $P < .01$) adjusting for CD4 level and CDC disease stage.

TABLE III. Features Comprising a TMA-Like Syndrome*

Schistocytosis (grade)	
0/1	266 (82%)[a]
2	84 (18%)
Neurologic	
Motor deficit	86 (25%)
Sensory deficit	86 (25%)
Cognitive deficit	53 (15%)
Seizure	17 (5%)
Headache	99 (28%)
Fever (⩾37.5°C)	203 (58%)
Proteinurea (⩾1 + protein)	158 (45%)
Hematuria (⩾1 + hemoglobin)	28 (8%)
Creatinine >1.4 mg/dl	92 (26%)
Any renal disease	239 (68%)
Thrombocytopenia (<150,000/mm^3)	103 (29%)
Anemia (<11 g/dl women, <12 g/dl men)	221 (63%)
Anemia + thrombocytopenia + schistocytosis (group 1)	27 (8%)
Group 1 + renal disease	22 (6%)
Group 1 + neurologic + fever	8 (2%)
Group 1 + renal or fever + neurologic (TMA-like syndrome)	25 (7%)

*TMA, thrombotic microangiopathy.
[a]Number (%).

CONCLUSIONS

Grade 2 schistocytosis occurred in 24%, and a TMA-like syndrome occurred in 7% of the HIV-infected patients admitted to the Johns Hopkins Hospital consecutively from May 1, 1996 through February 1, 1997. Patients with more advanced immunosuppression as measured by CD4 count or CDC disease stage had the highest frequency of grade 2 schistocytosis and of a TMA-like syndrome. In addition to the triad of thrombocytopenia, anemia, and schistocytosis, renal dysfunc-

TABLE IV. Association of TMA-Like Syndrome With Patient Characteristics*

Patient characteristics	TMA-like syndrome: Yes (N = 25)	TMA-like syndrome: No (N = 325)	*P* value
Age (years)	40 ± 7[a]	39 ± 7	.59
Sex			
Male	20 (80%)[b]	222 (68%)	.22
Female	5 (20%)	103 (32%)	
Race			
White	4 (16%)	50 (15%)	
African American	20 (80%)	266 (82%)	.93
Other	1 (4%)	9 (3%)	
HIV risk group			
IDU	13 (52%)	193 (60%)	.45
Homosexual	6 (24%)	75 (23%)	.93
Heterosexual	11 (44%)	121 (37%)	.52
Other	2 (8%)	20 (6%)	.72
CDC stage			
A	0 (0%)	8 (2%)	.007
B	1 (4%)	89 (27%)	(trend)
C	24 (96%)	228 (71%)	
CD4 (cells/mm^3)	32 ± 44	112 ± 9	.0001
CD4 percent	4.9 ± 6.4	9.3 ± 10.4	.007
HIV-1 RNA (copies/ml)	369,000 ± 332,000	218,000 ± 280,000	.17
White blood count (/mm^3)	5406 ± 6361	5689 ± 3818	.83
Absolute neutrophil count (/mm^3)	4317 ± 5492	4232 ± 3719	.94
AST (IU/L)	60 ± 46	66 ± 90	.59
ALT (IU/L)	31 ± 26	42 ± 52	.09
Total bilirubin (gm/dl)	0.9 ± 1.5	0.9 ± 1.6	.92
Albumin (gm/dl)	3.0 ± 0.9	3.4 ± 0.8	.06
Died within 30 days	6 (24%)	18 (6%)	.003
Length of hospital stay (days)	9 ± 5	9 ± 22	.82

*TMA, thrombotic microangiopathy; HIV, human immunodeficiency virus; IDU, injecting drug use; CDC, Centers for Disease Control and Prevention; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]Mean ± standard deviation.
[b]Number (%).

tion was the most frequent concurrent clinical feature. Neurological dysfunction and fever were less common.

The pathophysiology of a TMA-like syndrome is unknown. It has now been described in over 150 HIV-infected patients in the literature [5], though our results would suggest that it is far more common when searched for actively. In particular, schistocytosis on peripheral blood smear is quite frequent (24%) in hospitalized HIV-infected patients, but providers are likely to be unaware of this high frequency because the peripheral blood smear is not commonly examined.

Whether this high frequency of a TMA-like syndrome in advanced HIV disease is a direct consequence of the virus, or due to some other mechanism such as cytokine dysregulation or possibly immune suppression facilitating infection with other organisms is not known, although we did find that bacterial sepsis was associated with a TMA-like syndrome in our population. Infection with *Escherichia coli* (*E. coli*) 0157:H7 have been recognized as being associated with TTP [7]. *E.coli* was not an infecting organism in any of our patients with a TMA-like syndrome. No particular drug was found to be associated. In a prior study of prevention of cytomegalovirus disease (ACTG 204), valacyclovir was associated with a TMA-like syndrome in 18 patients [8]. No patient in our study received valacyclovir, and acyclovir use was not associated with a TMA-like syndrome in this sample. Fluconazole was associated with TMA in one earlier study [9], but was not associated in our study.

Notably, death was more frequent in patients with a TMA-like syndrome than in other patients. Although it is possible that a TMA-like process may have contributed to a poor outcome, these patients were also more likely to have more advanced immunosuppression. However, a TMA-like syndrome was independently associated with dying after adjusting for the CD4 level and disease stage. During the course of this study, no patient was diagnosed with or treated specifically for TTP or HUS. This independent association with death does not imply that treatment for TMA would have altered the outcome. A TMA-like syndrome may be part of a terminal process in some HIV-infected patients.

It should be noted that our detection of fragmented erythrocytes was done by a qualitative evaluation of the

TABLE V. Association of TMA-Like Syndrome With Drugs Received and Diagnoses[†]

Drugs received and Diagnosis	TMA-like syndrome Yes (n = 25)	TMA-like syndrome No (n = 325)
Drugs received (>5% of TMA patients)		
Fluconazole	7 (28%)[a]	79 (24%)
Stavudine	6 (24%)	46 (14%)
Trimethoprim-sulfamethoxazole	10 (40%)	180 (55%)
Lamivudine	6 (24%)	92 (28%)
Zidovudine	4 (16%)	96 (29%)
Acyclovir	2 (8%)	29 (9%)
Dapsone	4 (16%)	53 (16%)
Nortriptyline	3 (12%)	7 (5%)
Didanosine	2 (8%)	10 (3%)
Diagnosis		
Pneumocystis carinii pneumonia	2 (8%)	31 (10%)
Cryptococcal disease	3 (12%)	8 (2%)
Bacterial sepsis	6 (24%)	30 (9%)*
Mycobacterium avium bacterium	1 (4%)	4 (1%)
Toxoplasmosis	1 (4%)	4 (1%)
Cryptosporidiosis	1 (4%)	1 (<1%)
Varicella retinitis	2 (8%)	0 (0%)
Stevens-Johnson syndrome	1 (4%)	1 (<1%)
Pancreatitis	1 (4%)	1 (<1%)
Kaposi's sarcoma	1 (4%)	1 (<1%)
Bacterial peritonitis (no sepsis)	1 (4%)	0 (0%)
Bacterial pneumonia (no sepsis)	1 (4%)	36 (11%)
Cytomegalovirus colitis	1 (4%)	2 (<1%)
Myobacterium Kansasii pneumonia	1 (4%)	2 (<1%)
Subdural hematoma from trauma	1 (4%)	0 (0%)
Pulmonary aspergillosis	1 (4%)	1 (<1%)

[†]TMA, thrombotic microangiopathy.
*$P < 0.02$. All other comparison had P values >0.05.
[a]Number (%).

peripheral blood smear in the Johns Hopkins Hospital Hematology Laboratory. Quantitation of the specific number of fragmented cells per high-powered field was not done. It is possible that the frequency of schistocytosis might be somewhat different based on a specific quantitation of fragmented cells. However, our experience in our hospital suggests that a more detailed quantification would have yielded similar results.

In summary, qualitatively moderate schistocytosis is relatively common in hospitalized patients. A TMA-like syndrome is less common, but certainly not rare. Although TTP was not diagnosed in any of these patients and no specific treatment for TMA (e.g., plasma infusion or plasmapheresis with plasma exchange) was given to these patients, it may be important to recognize the relatively high frequency of schistocytosis and TMA-like syndromes as a complication of advanced HIV infection.

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